EXHIBIT 29

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327 MDL 2327** **JOSEPH R. GOODWIN U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 3 Cases*	

EXPERT REPORT OF CATHERINE A. MATTHEWS, M.D., FACOG

I. Qualifications

Background and Education

I am a Professor of Obstetrics/Gynecology and Urology and Co-Director of an Integrated Pelvic Health Unit at Wake Forest University Medical Center in Winston Salem, NC. I received my general Obstetrics and Gynecology Board Certification in 2004 and passed the first written board examination that was offered for sub-specialist certification in Female Pelvic Medicine and Reconstructive Surgery (FPMRS) in 2013. I was selected to serve as 1 of 8 national experts to administer the first oral board examination for FPMRS in 2015. This board certification is a critical step in standardizing the clinical and surgical knowledge required to provide appropriate care for women with pelvic floor disorders including establishing a certain level of knowledge and expertise that is required for new pelvic floor surgeons regarding potential complications of synthetic midurethral slings. I am licensed to practice medicine in North Carolina.

I received my Doctorate of Medicine from the University of Virginia, graduating as Valedictorian in 1997. I completed my Internship and Residency in Ob/Gyn at Virginia Commonwealth University (VCU) in Richmond, Virginia. During my residency, I trained under the renowned Urogynecologist, W. Glenn Hurt, who was an early president of the American Urogynecology Society and a pioneer in female pelvic medicine. Upon graduation, Dr. Hurt recruited me to join the faculty at VCU as an Assistant Professor in the division of Urogynecology. Under his tutelage, I received advanced training in female pelvic medicine and assumed care of his large referral practice 3 years later upon his retirement. Dr. Hurt was an avid proponent of Burch colposuspension and autologous pubovaginal slings for stress incontinence and through his supervision, I gained expertise in surgical management of this condition. I have independently performed approximately 85 Burch procedures and 50 pubovaginal slings.

At VCU, I achieved excellence in scholarship and teaching and was promoted from Assistant to Associate Professor within 5 years. In 2010, I was recruited to serve as the Division Chief of Urogynecology at the University of North Carolina in Chapel Hill, NC. There I expanded the division from 4 to 7 faculty members and added a strong research infrastructure that resulted in numerous clinical research trials. In September of 2015, I accepted a joint faculty appointment as Professor of Urology and Ob/Gyn at Wake Forest University following my engagement to a resident of Winston Salem.

Through consistent academic contributions to this field, I have developed an international reputation as an expert in female pelvic medicine and have been invited to lecture at prominent national conferences such as the American Urogyecology Fellows' course and the American Urology Association annual clinical update; chaired numerous workshops at AUGS, AAGL, and IUGA; and have delivered over 50 invited international lectures. In addition, I have been invited to demonstrate live surgery in Italy, Argentina, South Africa, and Brazil. My

commitment to teaching has been rewarded with more than 20 local and national teaching awards.

I have published over 60 peer-reviewed articles on subjects that include surgical techniques of robotic prolapse repair, novel treatment options for fecal incontinence, utility of mesh slings at the time of robotic sacrocolpopexy, and outcomes of different techniques of prolapse repair. In 2015, I was the second author on a paper that received the Pitkin award for "Top Paper in Obstetrics and Gynecology". This paper, which also was rewarded the "Best epidemiology paper" at the 2013 AUGS annual meeting, details the lifetime risk of prolapse or incontinence surgery for women in the United States. My ability to understand and critique the medical literature is reflected in being awarded the "Top 5% reviewer" prize by the American Journal of Ob/Gyn. I also regularly serve as a peer reviewer for Obstetrics and Gynecology, the International Urogynecology Journal, and the British Medical Journal. These academic contributions demonstrate my commitment to the pursuit of evidence-based practice.

In 2011, I was voted onto the Board of the American Urogynecology Association (AUGS) as the Vice-Chair of the Foundation and then assumed Foundation Chair in 2013. While serving on the AUGS Board, I was intimately involved in the extensive discussions surrounding the use of mesh for incontinence and prolapse repair and was involved in the drafting, editing, and release of the AUGS-SUFU position statement on sub-urethral mesh slings for stress incontinence treatment. Based on a survey of AUGS members of whom 99% endorsed use of mid-urethral slings for stress incontinence management (Clemons, 2013) the Board attached the highest importance to this statement. We felt obligated to carefully and objectively review the relevant literature regarding safety and efficacy and provide a position statement that reflected majority membership practice and could be relied upon as the best available evidence and best practice by our membership.

I am currently engaged in international leadership as chair of the Education Committee of the International Urogynecology Association and continue to serve as a sub-specialty board examiner for the American Board of Obstetrics and Gynecology. My current research portfolio includes the use of stem cell therapy for stress incontinence, translational studies for fecal incontinence, and surgical techniques for pelvic floor repair.

For additional information about my qualifications as an expert in female pelvic medicine and reconstructive surgery, please refer to my attached Curriculum Vitae.

Clinical experience

Over the past 15 years, I have dedicated my career to improving the lives of women suffering from pelvic floor disorders. I achieve this goal through my direct patient care and through my life-long commitment to the surgical training of residents and

fellows. I was fortunate to quickly accrue clinical and surgical experience through the wide referral network that my mentor established at VCU. Our high volume surgical practice gave me exposure to the most complex and interesting cases for both prolapse and urinary incontinence. Upon transfer to UNC, I further expanded my clinical footprint by building 2 pelvic health centers that served as tertiary care referral centers for complex cases. While coordinating our whole program, I personally maintained a very high-volume surgical practice for women with pelvic organ prolapse, urinary incontinence, and fecal incontinence, performing more than 250 major cases annually. My case volume consists of all procedures for female pelvic floor reconstruction, namely vaginal hysterectomy, high uterosacral ligament suspension, sacrospinous ligament fixation, sacrospinous hysteropexy, native tissue repair of the anterior and posterior vaginal walls, non-trocar based mesh augmented repairs of the anterior vaginal wall and apex, colpocleisis, and robotic sacrocolpopexy. For stress incontinence, I am trained to perform mid-urethral slings (retropubic and transobturator slings), retropubic colposuspensions, autologous pubovaginal slings, and urethral bulking injections. Finally, I have built a wide referral practice for the management of all mesh-related complications including erosions into the bladder, urethra, rectum, and vagina and vaginal/pelvic pain. At UNC, I established a joint clinic with the pelvic pain division to serve women with any mesh related pelvic pain syndrome. While the vast majority of patients seen in this clinic had pain following vaginal mesh for prolapse repair, we did evaluate a small sample of women with pain following sling procedures.

My clinical experience has always included the training of medical students, residents, and fellows in the conservative and surgical management of pelvic floor disorders. I believe that my greatest contribution to women is through high quality education. I am tasked with teaching trainees appropriate case selection, procedural techniques, how to avoid and manage surgical complications, appropriate post-operative care and follow up, and how best to practice evidence-based medicine for all procedures that treat pelvic floor disorders. Additionally, I have extensive experience teaching residents and fellows on the risks and benefits of surgical treatment for stress urinary incontinence and pelvic organ prolapse, including training on the Instructions for Use (IFU). Regarding my specific clinical experience with training residents and fellows in surgical management of stress incontinence, both the Accreditation Council for Graduate Medical Education and the American Urological Association list competencies and objectives for teaching synthetic mid-urethral slings, pubovaginal slings, and colposuspension procedures. All general ob/gyn and urology residents are also required to demonstrate competency in the placement of mid-urethral slings prior to graduation. Thus, I have an intimate understanding of what the reasonably prudent pelvic floor surgeon should know about the risks and benefits of pelvic floor procedures, the adequacy of the warnings in IFUs, the management of mesh complications, and the well-known risks that are associated with any pelvic floor surgery. It is well known by all pelvic floor surgeons that any surgery for stress urinary incontinence or pelvic organ prolapse, with or without the use of mesh, can potentially cause complications that can be temporary or permanent, including but not limited to: pelvic pain, dyspareunia

(pain with sexual intercourse), scarring, vaginal narrowing, leg/groin pain, urinary retention and other voiding problems. These complications, and general complications associated with foreign body graft materials, such as mesh erosion or exposure, have been documented in the medical literature for decades.

At present, I am the Co-Director of a new Integrated Pelvic Health Unit that is tasked with the development of a multidisciplinary service line for the state-of-the-art care of women with pelvic floor disorders. I am assigned to clinical and teaching responsibilities 90% of the week with administrative/research time protected at only 10% effort. My clinical time is divided into 1.5 days of surgery and 3 days of clinic during which I care for women with pelvic organ prolapse, urinary incontinence, fecal incontinence, mesh exposure, pelvic pain, dyspareunia, hematuria, recurrent urinary tract infections, and any complication following prolapse or urinary incontinence surgery.

Personal experience with use of mid-urethral slings

While my current practice strongly endorses the use of polypropylene mid-urethral slings for the management of stress incontinence, I was not an early adopter of these devices. Despite FDA clearance in 1998, I was initially reluctant to implant any sling device as I was concerned about the risks of a foreign body that could be difficult to remove and was not comfortable about my level of knowledge of material science. Furthermore, my mentor was a firm advocate of evidence-based medicine and would not entertain the use of synthetic slings until comparative evidence, with a full investigation of associated risk and benefit, was available. Following his lead, I refused to accept the early enthusiasm for "quicker and easier".

Two things significantly changed my clinical practice: 1) Publication of Level I comparative evidence demonstrating equivalence of the TVT retropubic sling to the Burch colposuspension, with fewer associated complications including less blood loss, pain, voiding dysfunction, days of catheter use, time in the hospital, and time to return to normal activities, and 2) Improved familiarity with the specific mesh properties of the TVT sling including pore size, tensile strength, and durability that assured me as the implanting surgeon that the device itself was safe for use. Surgeons are required to obtain knowledge of all new devices and surgical instruments prior to use and should not rely on industry representatives for education (Matthews, 2009). In my practice, I now predominantly perform retropubic slings but select transobturator slings in women with voiding dysfunction or risk factors for severe intra-abdominal adhesive disease. I have performed over 500 slings in my career thus far, most of which have been Ethicon's TVT device. Within this device category, I have not personally witnessed any differences in outcomes between meshes that were mechanically cut or laser cut.

Since the introduction of mid-urethral slings into my surgical practice, my annual rate of Burch and pubovaginal slings has fallen dramatically to approximately 5 and

2, respectively. I continue to recommend the Burch procedure to any woman who is already undergoing laparotomy. I recommend a pubovaginal sling to women with a history of pelvic radiation, severe refractory stress incontinence, or prior complication from a mid-urethral sling such as urethral mesh erosion. I teach all 3 types of incontinence procedures to my trainees in urology and Ob/Gyn. While all 3 surgical options are offered to every single surgical candidate, it is rare that a woman with primary stress incontinence accepts the greater surgical morbidity and voiding dysfunction of either the Burch or pubovaginal sling.

My personal experience with mid-urethral slings mirrors the widely published results of 80-85% efficacy with 2-4% sling revision rate for mesh exposure and voiding dysfunction. I select this option as the first line surgical treatment for stress incontinence that has failed conservative treatment. Based on slightly improved efficacy, I typically choose retropubic as compared to trans-obturator slings unless women have a significant risk of voiding dysfunction, intra-abdominal adhesive disease, or bleeding risk- in these women, I believe that TOT slings carry lower risk. I quote personal efficacy rates of 85-90% in women with hypermobility and about a 65% cure rate in women with intrinsic sphincter deficiency. While on a continuum of urethral dysfunction/poor urethral coaptation, intrinsic sphincter deficiency (ISD) presents the worst extreme and is distinguished from "typical" SUI with absence of urethral hypermobility and lower valsalva leak point pressures. It is well documented that women with ISD demonstrate higher efficacy with TVT compared to TOT slings and a lower overall efficacy compared to women without a diagnosis of ISD (Ford, 2015; Rezapour, 2001). Historically, autologous fascial pubovaginal slings were used as the standard treatment for ISD.

With the advent of minimally invasive procedures, currently the most favored treatment for both SUI and ISD-associated SUI is the midurethral sling (MUS). A 2015 systematic review and meta-analysis found that while midurethral slings are effective in treating women with intrinsic sphincter deficiency-associated stress urinary incontinence, the retropubic route resulted in higher subjective cure rates compared with transobturator routes. However, both routes improved the overall quality of life. (Ford, 2015) My personal sling revision rate is approximately 1.5%. For slings that I have implanted, I have released 2 for acute voiding dysfunction and have noted less than 5 mesh exposures. Only 1 has required surgical revision in the operating room. When training residents and fellows, I can report a bladder perforation rate of 5-10% but this rate is less than 2% when I personally place the sling. I have never had a bladder or urethral mesh erosion, retropubic hematoma, vascular or nerve injury, or bowel injury. I have treated one patient with retropubic/groin pain following TVT and one following TOT. Neither required surgical intervention and in both cases, pain resolved with conservative medical management. I have never received payment from a device manufacturer for physician training on the use of slings and have never served as a consultant for Johnson & Johnson. In 2013, I did serve as an expert witness for American Medical Systems in defense of cases involving their retropubic and transobturator sling

products. Fees collected from this work were paid directly to UNC Healthcare System.

II. Materials reviewed

In preparation for my opinions that are drafted within this document, I performed a literature search and reviewed the medical and scientific literature pertaining to the use of mid-urethral slings (retropubic and transobturator) for stress incontinence management. These articles address topics that include device efficacy, safety, comparative effectiveness, surgical technique, material science/properties, and potential long-term complications. I have also reviewed the Ethicon TVT Instructions for Use (IFU), the professional educational materials that Johnson & Johnson provided to implanting surgeons, the TVT surgeons' resource monograph and other documents provided by Ethicon. I have also extensively reviewed monographs/position statements / systematic reviews / practice bulletins prepared by AUGS, SUFU, IUGA, AUA, SGS, and ACOG. A list of all reviewed materials and those that I may use at trial are attached to this report. I have also reviewed the plaintiff's expert reports including Drs. Blaivas, Elliott, and Rosenzweig. I reserve the right to supplement my report to the extent any new literature, records, or documents are made available for me to review.

III. Fees and Expert Testimony

My fees for serving as an expert in this matter are:

Chart review/ report drafting/ literature review/ meetings	$550/hr
Deposition testimony	$750/hr
Trial testimony	$8000/day

IV. Opinions

I was asked to provide my opinions on the safety of the design of TVT, as well as the adequacy of the warnings in the Instructions for Use in the matter of In re: Ethicon, Inc. Pelvic Floor Repair System Products Liability Litigation, MDL No. 2327, which is currently pending in the Southern District of West Virginia. Outlined below is an explanation of my opinions and the medical rationale for these opinions. They are based on my education, training, extensive medical reading, professional experience, observation of colleagues, participation in local, national and international meetings, participation on the AUGS board, and a comprehensive review of published scientific papers and position statements, discussions with colleagues, and experience training medical students, residents, and fellows. All of my opinions are

held to a reasonable degree of medical probability. In summary, in my opinions discussed below, the TVT's design and material is reasonably safe for its intended use and the Instructions for Use adequately and appropriately warns physicians trained in the surgical treatment of stress urinary incontinence of the potential adverse reactions associated with the device.

A. Overview of stress urinary incontinence (SUI)

SUI is the involuntary loss of urine with any increase in intra-abdominal pressure such as coughing, sneezing, or exertion that results from faulty closure of the urethra. Typically, a spurt of urine is released from the urethra during increased intra-abdominal pressure. It affects up to 1/3 of all women and about 14% will have severe enough incontinence to undergo surgery in their lifetime (Wu, 2014). For perspective, a woman's lifetime risk of developing breast cancer is 14.8%, whereas the lifetime risk of lung cancer is 6.3%.

SUI is often a debilitating and bothersome condition that can substantially reduce a woman's quality of life. For example, a young patient of mine recently remarked: "I find myself sadly watching my children from the sidelines- I just want to be able to confidently join in and play with them again." Another patient expressed extreme embarrassment and frustration when she leaked all over her shorts at the gym: "How can I possibly exercise and lose weight when it is clear to everyone around me that I'm peeing on myself." Although non-surgical treatments such as pelvic floor exercises, vaginal pessaries, and behavioral modification are helpful in alleviating symptoms in some women (Imamura, 2010), many proceed with surgery. When surgery is directly compared to pelvic floor physical therapy, it is found to be a more effective treatment (Labrie, 2012).

Mid-urethral slings have revolutionized the surgical approach to SUI management. Historically, the surgical options included retropubic colposuspension (Burch procedure and the MMK) and autologous pubovaginal slings. Both procedures require "direct access" to the tissues surrounding the bladder and urethra and are deemed "major" surgical cases that involve an abdominal incision and wide vaginal dissection. This extensive surgery is associated with a significant risk of wound complications, bleeding, and genitourinary tract injury including damage to the ureter, bladder, and urethra (Stanton 1985). Urinary tract injuries have been reported to occur in 6.3% of pubovaginal sling procedures (Summitt, 1992) and in up to 9% of Burch procedures (Stevenson 1999). Wound complications, particularly in overweight women, are a major issue (Albo, 2007). Additionally, Demirci et al. reported long-term complications of post-operative groin or suprapubic pain (6.8%) and dyspareunia (2.7%) after the Burch procedure. The 2012 AUA Guidelines Appendices and the SGS 2014 Meta-Analysis also provide detailed complication rates for the Burch and Autologous fascial slings compared to synthetic midurethral slings. Median surgical times are typically in excess of 2 hours, hospital stay averages 2-3 days, and prolonged catheter drainage is usually required. Most of my

young, ambulatory women with primary stress incontinence are unwilling to take 6 weeks off from work and their family obligations to recover from these surgical interventions. While one can directly measure the economic impact of 4-6 weeks of lost wages and productivity, women find it difficult to assess the price of not being able to effectively care for their family members during their convalescence from a major procedure for SUI.

Besides acute intraoperative complications, the post-operative risk of voiding dysfunction is remarkably high with some studies reporting an incidence of up to 25% (Parnell, 1984; Galloway 1987; Lose 1987; Erikesen 1990). Women are often more bothered by the inability to empty the bladder effectively than the original complaint of urinary leakage. The reason that both procedures are associated with difficulty emptying the bladder is they provide constant, "static" support and elevation of the bladder neck at rest and during increased intra-abdominal pressure. Late term complications also include the development of pelvic organ prolapse due to the change in angulation of the vagina with the colposuspension sutures with associated symptoms of pain with intercourse (Demirci, 2001). In my practice, because of the surgical morbidity and long-term associated risks of these 2 options, women had to objectively demonstrate a severe case of SUI before I would subject them to either operation. It has always been my firm belief that when dealing with a quality of life condition, the obligation to minimize risk takes a priority over curing the condition. For women with severe or refractory urinary incontinence, I certainly agree that pubovaginal slings are a viable surgical option.

In addition to the risk of complications, neither historical option has been associated with cure rates that are consistently sustained over time. The largest randomized trial comparing autologous pubovaginal sling to Burch colposuspension in 655 women (SISTEr trial) initially reported 2-year success rates (no self-reported SUI symptoms, a negative stress test, and no retreatment for SUI) of 66% in the pubovaginal sling group and 49% in the Burch group. At 5 years post-surgery, the success rate (defined as no symptoms of urinary incontinence on a questionnaire and no retreatment for SUI) had dropped to 34% in the sling group and to 24% in the Burch group. At 7 years, there was a further decline to 27% and 13%, respectively, with a corresponding effect on patient satisfaction (Richter, 2011). Therefore, less than 1 out of 4 women subjecting themselves to these major procedures can expect to be dry within 7 years of the initial operation. These results have been corroborated by numerous authors, most recently Kjolhede et al who reported that at 14 years post-procedure, only 19% of 190 women remained completely dry and 56% demonstrated significant leakage (Kjolhede, 2005).

B. Advent of tension-free mesh slings (TVT) for SUI

The combination of high surgical morbidity, poor long-term efficacy, and unacceptable rates of voiding dysfunction presented a clear opportunity for surgical innovation. An obvious treatment gap existed and there was a need to find a surgical

intervention where the cure was not worse than the disease. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment.

Pelvic floor surgeons began looking for substitutes for fascial slings decades ago. Williams and TeLinde published their use of a Mersilene sling for treating urinary incontinence in 1962. These authors noted that the "Mersilene ribbon shortens and simplifies the operation by making it unnecessary to produce a full-length fascial strip, and only a short transverse suprapubic incision is necessary." Moir and colleagues described their use of a Mersilene "tension-free" sling in 1968. Morgan published on his results using Marlex polypropylene mesh in sling operations in 1970. He described how "most pelvic floor surgeons are familiar with the particular complications of pelvic scar," as well as post-operative complications that can be caused by excessive tensioning on the sling. Morgan clearly described voiding difficulties, such as retention and urgency, as a potential post-operative complication of any incontinence sling made of synthetic or autologous material..

Numerous other pelvic floor surgeons have published, going back decades, their use of synthetic slings and their associated complications. For example, Ridley in 1966 reported complications with Mersilene ribbon, including erosion into the bladder and recurrent stress incontinence. Dr. MacFarlane commented on Dr. Morgan's 1970 Marlex sling study, noting that "Most surgeons have been reluctant to use any foreign material prosthesis because of their fear of wound complications, infections, and tissue rejection." Dr. Nichols published his experience with Mersilene mesh sling operations in 1973 and noted "[i]n no instance, to date, in this case series has the urethra or bladder been injured. There has been no evidence of extrusion of the Mersilene or a sinus tract formation." Similarly, Dr. Fred Bryans published his experience with Marlex sling operations in 1979, and described "nonhealing of the vaginal wall" in five patients, which required the exposed portions to be excised in two patients. He also described two women who complained of post-operative dyspareunia and four women who experienced postoperative wound infection. Drs. Summit and Ostergard, and colleagues published their experience with PTFE slings in 1992, and described complications such as obstructed voiding, re-operation to loosen two slings due to voiding difficulty, and erosion that required removal of the graft. Further, in 1993, Drs. Bent and Ostergard published their 23% reaction or removal rate with ePTFE suburethral sling procedures, and concluded that "[p]atients needs to be aware of the high complication rates for this suburethral sling procedure, and physicians need to work further to modify sling materials and techniques to reduce complications." Dr. Young and colleagues published in 1995 their results with a Mersilene mesh sling, and reported erosion of the sling in two women, one of whom required removal of the mesh. They described the benefits of using a synthetic material over a patient's own tissues, but noted how "the success of synthetic slings has been marred by several reported complications, including infection, prolonged urinary retention, and graft rejection." Additionally, Dr. Norris and colleagues published their results with synthetic slings in 1996. The authors

discussed how "[i]nfection and erosion of these materials into the bladder, urethra, and vagina have been the principal risk factors associated with their use," describing a variety of sling materials that had been used for sling operations at that time, including Marlex, Silastic, Mersilene, Teflon, and GoreTex. This is by no means an exhaustive list of the early studies describing complications associated with synthetic slings, but it does show how complications associated with synthetic slings have been documented in the medical literature, and well known by surgeons performing these incontinence procedures, for decades.

The introduction of the TVT sling was facilitated by a paradigm shift in our understanding of the pathophysiology of SUI from a focus at the bladder neck to the functionality of the mid-urethra. The "Integral Theory", published by Petros and Ulmsten in 1990, described the critical interaction between the pubourethral ligaments supporting the mid-urethra, the levator ani muscles, and the elastic anterior vaginal wall. In essence, Petros outlined that continence is maintained when the pubourethral ligaments and pubococcygeus muscles contract during increased intra-abdominal pressure and the mid-urethra is compressed against a stable anterior vaginal wall, thereby closing the elastic urethal lumen. Focus on a new surgical cure was therefore directed away from providing static support to the bladder neck to rather providing dynamic support at the mid-urethra. The concept of introducing a stable platform of support, against which the mid-urethra could be compressed during increased intra-abdominal stress, was born.

In addition to a procedure that would provide better efficacy and lower rates of voiding dysfunction, there was a desire to find a solution that was "minimally invasive", that did not require a major incision, could be done under local anesthesia, and would require a shorter recovery time. In 1996, Professor Ulmsten and colleagues published their 2-year outcomes of a new sling termed the intravaginal slingplasty (IVS) in 75 women. The IVS consisted of a synthetic, polypropylene sling that was introduced through a small vaginal incision into the retropubic space using metal trocars. Importantly, the mesh sling was placed in a completely tension-free manner with no static elevation or support of the urethra. The procedure was done under local anesthesia with a mean operative time of 22 minutes. At 2 years, there were no reported cases of mesh erosion or other major postoperative complications and a cure rate of 84% was achieved (Ulmsten 1996). Based on these early encouraging results, Ulmsten and colleagues worked with Johnson & Johnson to modify the sling that was then introduced to the market in 1998. It is important to note that any potential for bias associated with Ulmsten's initial studies is obviated by the fact that Ulmsten's initial and long-term results have been reproduced and corroborated time and time again in well over 100 randomized controlled trials, and in hundreds of clinical studies evaluating the safety and efficacy of TVT, even well after Professor Ulmsten's death in 2004.

C: Safety of the design of the TVT

The fundamental goals of this novel incontinence procedure were:

1. To avoid the need for a major abdominal incision and use the vagina as the primary route of surgical access

2. Introduce a stable hammock of support at the level of the mid-urethra and not the bladder neck

3. Provide urethral closure only during episodes of increased intra-abdominal stress and not at rest, thereby reducing the risks of voiding dysfunction

4. Use a sling material that was safe, durable, and did not require harvesting of native tissue

5. Design a system that required minimal tissue dissection, thereby maximally preserving the nerves and surrounding supportive tissue.

6. Design a procedure and technique that is highly reliable and reproducible.

The evolution of the TVT sling was based on sound, scientific evidence that corrective procedures needed to focus on the mid-urethra rather than on the bladder neck. In my opinion, it was a strategically brilliant solution that resulted from an innovative deviation from the traditional model of thinking about SUI treatment. This new surgical approach incorporated some of the traditional elements of incontinence surgery, such as the vaginal approach of the traditional pubovaginal sling, but introduced 3 entirely new concepts: Minimal dissection, no direct suturing of the sling to any anchoring point, and placement of the sling in a completely tension free manner.

As the female urethra is 3-4 cm in length, designing a sling with a 1.1 cm wide strip of mesh permitted direct and isolated support at the mid-urethra. Instead of performing a complete dissection of the para-urethral and retropubic spaces, the design incorporated surgical trocars that can traverse the space, much like the needles used in the Raz and Stamey procedures. The "bottom up" approach allowed for the precise placement of the sling at the mid-urethra and avoided the need for a full para-urethral dissection to retrieve the sling as was required for any traditional pubovaginal sling. Instead of having to close a major abdominal incision, only small exiting trocar sites required closure, something that can be accomplished with 1 suture or with skin glue. A recent Cochrane Review discussed the benefits of a bottom-up approach over a top-down retropubic approach. (Ogah 2011). Finally, the system was designed as an "anchorless" sling whereby the mesh itself inter-collated into the host tissue instead of being directly anchored to the pubic bone or rectus fascia. Prior anchoring techniques were associated with a host of serious problems including osteomyelitis, pain, and voiding problems. All of these new features were designed to maximize functionality of the sling while minimizing surgical morbidity and postoperative voiding dysfunction.

Due to the absence of a major abdominal incision and limited dissection, the procedure was also amenable to local as opposed to general anesthesia. In fact, all of the patients in the original cohort were performed with local anesthetic only. It is widely accepted that local anesthesia is significantly safer, cheaper, and allows the patient to cough if needed to adjust the sling tension.

The reproducibility and "teachability" of the procedure, broken down into a clear series of surgical steps, was demonstrated through a systematic training program of all surgeons in Finland who wished to use the TVT. Results of this study, which detailed outcomes of 1455 patients, demonstrated how a standardized training program can achieve optimal outcomes (Kuuva, 2002).

When looking for the best material to use for implantation, the desired properties included:

1. Low risk of host "rejection"
2. Low risk of mesh infection
3. Minimal host tissue inflammatory response
4. Maximum host tissue ingrowth into the mesh
5. Absence of cytotoxicity
6. No risk of carcinogenesis
7. Sufficient tensile strength to not break
8. Stability of mesh product over time

In 1994 and 1997, Amid categorized synthetic materials used in abdominal hernias based on their properties including pore size, fiber type, and fiber architecture. This classification improved our understanding of properties that maximized tissue ingrowth and minimized the risk of mesh infection and exposure. Type I mesh is monofilament and manufactured with a pore size greater than 75 microns. Type II mesh is also monofilament but with smaller pore size that allow for bacterial infiltration but are not large enough to permit angiogenesis or fibroblast incorporation. This results in a significantly higher rate of mesh infection. Type III mesh is woven in a manner that permits bacterial proliferation but no host factor response and is therefore associated with much higher rates of mesh infection and rejection. Type IV meshes are sub-microporous coated biomaterials with pore size of less than 1 micron that are rarely used in our field. Amid described why the monofilament polypropylene mesh is superior to other available synthetic materials – "It is completely inert, resists infection and sinus tract formation, has rapid fibrinous fixation, becomes completely incorporated into the host tissue, and in case of infection does not have to be removed." In addition to the importance of a large pore size (greater than 75 microns), Amid noted the importance of surface texture and anatomical location. The Prolene TVT mesh is considered to be an Amid Type 1

mesh, and is commonly referred to as large-pore and lightweight mesh. (AUGS/SUFU 2014 Position Statement; Walters, Weber 2012 Which Sling for Which SUI Patient). Dietz and colleagues described in 2003 how synthetic slings "have recently become popular despite the risk of erosion commonly associated with synthetic implants." They noted, however, that "some of these materials seem to have unexpectedly low erosion rates." Dietz and colleagues compared the biomechanical properties of eight nonabsorbable synthetic implant materials, including stiffness and peak load. They found that the "open-weave Prolene mesh showed unique biomechanical properties compared to other tested materials," and that the TVT had the "lowest initial stiffness (0.23 N/mm), i.e., low resistance to deformation at forces below the elastic limit, whereas the stiffest implant tested, a nylon tape, reached 6.83 N/mm." The authors attributed the clinical success of TVT to these characteristics. Dietz and colleagues described the risk/benefit analysis with synthetic slings, in that the "advantage of superior strength and durability, easy availability and versatility compared to autografts such as rectus sheath or fascia lata has to be balanced against an increased risk of infection and erosion." The authors noted how no mesh sling has become more widely accepted worldwide as the TVT, which they attributed to the "very low likelihood of erosion, which is surprising given previous experience with synthetic slings." Moalli and colleagues published in 2008 on the tensile properties of five midurethral slings (Sparc/Monarc, Advantage/Obtryx, Aris, T-Sling, Uretex) compared to TVT/TVT-O mesh. Table 1 of the Moalli 2008 study compares the textile properties of the different slings, with TVT having the largest pore size out of all of the meshes at 1,379 microns. The table also includes measurements for mesh thickness, fiber size, weight, relative porosity, load at failure, and mesh edge features. Moalli and colleagues discussed how "a low stiffness material may also make the sling less likely to obstruct the urethra or cause postoperative voiding dysfunction," and suggested that postoperative complications of erosions and voiding difficulties may be less common after TVT due to TVT's biomechanical behavior.

Table 1 Classification of synthetic implant materials

	Component	Trade name	Fibre type
Type I: Totally macroporous	Polypropylene	Prolene, Gynemesh, Gynemesh PS (Ethicon)	Monofilament
		Marlex, Pelvitex[a] (Bard)	Monofilament
		Surgipro[b] SPMM (Tyco)	Monofilament
	Polypropylene/Polyglactin 910	Vypro (Ethicon)	Mono multifilament
	Polyglactin 910	Vicryl (Ethicon)	Multifilament
Type II: Totally microporous	Expanded polytetrafluoroethylene	Gore Tex (Gore)	Multifilament
Type III: Micro or macro micro	Polyethylene	Mersilene (Ethicon)	Multifilament
	Polytetrafluoroethylene	Teflon (Gore)	Multifilament
	Braided polypropylene	Surgipro[b] SPM (Tyco)	Multifilament
	Braided polypropylene open weave	Surgipro[b] SPMW (Tyco)	Multifilament
	Perforated Expanded Polytetrafluoroethylene	Mycro mesh (Gore)	Multifilament
Type IV: Submicronic pore size	Polypropylene sheet	Cellgard	Monofilament

Macroporous is defined as pore size >75 μm, microporous ≤75 μm
[a]Recently collagen coated macroporous polypropylene materials like Pelvitex (Bard) came on the market; their place, if any, needs to be defined
[b]Several kinds of Surgipro (Tyco) materials are marketed under the same name and have different constructs

Table taken from Deprest (2006).

Cosson and colleagues published an article in 2003 on the mechanical properties of synthetic implants used in the repair of prolapse and urinary incontinence. The authors noted that TVT "should be discussed separately, even though it could be integrated into a sling intervention," because the "remarkable tolerance of this Prolene strip is confirmed in the literature, with very few cases of rejections reported." Cosson and colleagues also discussed studies that demonstrated different complication rates based on the surface area of the synthetic material, thus helping to explain the difference in complication rates as seen in the SUI literature compared to the POP and hernia literature. Although there is literature evaluating "heavyweight" meshes in animals that suggests heavier meshes lead to more complications, a hernia study comparing "lightweight" Prolene Soft to "heavyweight" 3D max mesh in humans demonstrated no statistically significant difference between the two groups in the incidence of chronic groin pain at 3, 6, and 12 months. (Prakash 2016). By contrast, a hernia study evaluating "heavyweight" and "lightweight" polypropylene in rats found worse biocompatibility in the "lightweight" group compared to the "heavyweight" group. (Weyhe 2006). The authors concluded that "the amount of mesh was not the main determinant of biocompatibility (expressed as successful incorporation and diminished foreign body reaction) but the size of the pores." Additionally, the theory that an increased inflammation reaction is proof of chronic pain does not bear true in the stress urinary incontinence literature. A study evaluating the histopathology of excised midurethral sling meshes found that midurethral sling mesh excised for voiding dysfunction demonstrated elevated levels of inflammation compared to mesh that was excised for pain and/or mesh exposure. (Hill 2015).

Bazi and colleagues in 2007 evaluated the biomechanical properties and histologic changes to different polypropylene midurethral slings after implantation in rats. The authors concluded that "stiffness of TVT was significantly lower than that of each of the other three brands." They also found that the "TVT group showed a low inflammatory infiltrate, the least fibrosis among the groups, a moderate number of mast cells, and the least muscular infiltration," as well as good collagen filling. In discussing the histologic aspects of the meshes, the authors noted that "the advantage of PP [polypropylene] over other synthetic material, in regard to biocompatibility, has already been established in animal and human studies."

In 2015, Dr. Petros, who cofounded the intergral theory with Dr. Ulmsten, discussed the scientific discoveries leading to TVT, including a discussion about the early animal and human developmental studies. Petros and Ulmsten initially used a variety of synthetic materials and found that Ethicon's Prolene was the most suitable for what became the TVT. Petros noted how "Mersilene was easy to use, non-stretch, and effective, but it had a high erosion rate (14%)," and by 1996 polypropylene [Prolene] mesh tape had solved the problem of erosions and became "universally accepted."

Iglesia and colleagues discussed the use of mesh in gynecologic surgeries in 1997, and noted that while both Marlex and Prolene are both composed of knitted filaments of polypropylene, the two meshes are woven differently and Prolene has a larger pore size than Marlex (1500 vs. 600 microns). The authors describe "mesh-related complications" in Table 2A regarding suburethral slings using Marlex, including: obstruction, voiding dysfunction, poor vaginal healing, vaginal removal, sinus tract, urethral erosion, prolonged retention, and transurethral resection of the mesh. Similarly, the authors list in Table 3A the complications reported with Mersilene suburethral slings, including: removal for suprapubic abscess, bladder erosion, urethral erosion, graft infection, sling divisions for retention, Prolene suture exposures, voiding dysfunction, midvaginal band, and groin sinus. Similar results, such as graft erosions, rejections, revisions, and removals are reported for suburethral slings and Sacrocolpopexy procedures using Gore-Tex mesh in Table 4A and Table 4B.

Dr. Kobashi published in 2009 on the management of graft materials in pelvic floor reconstruction, and described how "the currently accepted, loosely woven, monofilament type I polypropylene meshes appear to have acceptable lower exposure rates in the range of 1-3% for slings, but with the larger area of mesh used in prolapse repairs, the rate increases to up to 10%." Dr. Kobashi explained how it is "imperative for surgeons to be familiar with potential complications related to the materials and proper management of these complications," as it appears that "the benefit of using some synthetic materials may outweigh the risks." In fact, in 2003, Dr. Kobashi published on the management of vaginal erosion of polypropylene mesh slings and stated that "erosion must always be considered a risk of synthetic materials."

Dr. Klinge, one of plaintiffs' materials experts, even noted the difference in using a large pore polypropylene mesh, like the Prolene in TVT. In 2010, Klinge published that "At present, the gold standard in SUI surgery is the suburethral sling, using either the tension-free vaginal tape (TVT) or the transobturator tape (TOT) technique." Dr. Klinge stated that the "initial concern that the meshes used might lead to high rates of erosion did not hold true when macroporous polypropylene was used," noting a 1.7% and 3.1% erosion rate in two long-term trials. Dr. Klinge described the difference in complication rates between an Amid Type 1 mesh (TVT) and an Amid Type 3 mesh: "A prospective randomized controlled trial by Meschia et al. showed that the vaginal erosion of the Amid type III mesh used for intravaginal slingplasty was as high as 9% in a 2-year follow-up, which is significantly higher compared to 0% using the classical TVT (type I macroporous, monofilament, polypropylene mesh) int eh same trial." In fact, Klinge has also published in 2004 that, "Today polypropylene meshes are the most commonly implanted meshes. Compared with other mesh materials, polypropylene has no tendency to degrade and shows sufficient integration into the surrounding tissues."

Dr. Choe published a book chapter in 2003 regarding the use of synthetic materials in pubovaginal sling surgery. Dr. Choe insisted that "if synthetic slings are used, the

surgeon must understand the strengths and weaknesses of the material used," and "if a surgeon chooses to implant synthetic slings, he or she must be willing to accept the responsibility of post-surgical complications and manage them appropriately." Dr. Choe concluded that synthetic slings do not appear to undergo deterioration over time. He also discussed how polypropylene mesh slings, such as Ethicon's Prolene, appear to have consistently lower erosion rates (0 to 3%) than other synthetic meshes. One of the benefits of the smooth monofilament is that bacterial attachment to the polypropylene is deterred. Most importantly, however, is that the Prolene mesh pores allow the host tissues to incorporate the synthetic mesh within the body to minimize infection.

The Ford 2015 Cochrane Review on midurethral slings stated that type I macroporous, monofilament polypropylene has been found to be the most biocompatible biomaterial for use in the pelvic floor.

The decision to use a polypropylene mesh material as the surgical implant was based on a record of safe human experience that was collected over 5 decades of use in a broad array of other surgical specialties including general surgery, transplant, urology, and otolaryngology. Dr. Usher first introduced knitted polypropylene mesh for hernia repairs in the 1960s. In fact, Ethicon's Prolene suture was originally approved as a Class III new drug application, but due to the high safety profile of polypropylene implants, the FDA down-classified polypropylene sutures and mesh to Class II in 1990. Type I monofilament, macroporous polypropylene mesh is the currently preferred synthetic material for human implantation as the large pore size facilitates infiltration of the mesh by macrophages, blood vessels, and fibroblasts. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery (Cobb, 2005; Scott 2002). Furthermore, polypropylene thread has long been relied upon as a permanent and durable surgical suture. There have been no associated cases of cancer directly related to the implant and no clinical or laboratory evidence of mesh degradation or cytotoxicity (King 2014, Moalli 2014, AUGS/SUFU FAQs by Providers, Stanford 2006, Woodruff 2008, de Tayrac 2011, Clave 2010, Liebert 1976).

The initial TVT trials with Prolene mesh showed no adverse reaction. Specifically, there was no indication of unacceptable rates of mesh infection, rejection, host tissue reaction, or impaired healing (Ulmsten, 1998). Biopsies of para-urethral tissues were assessed 2 years following implantation and no evidence of adverse host tissue reaction was found (Falconer, 2001). An evaluation of the biomechanical properties of the TVT implant also revealed this large pore polypropylene mesh had the lowest stiffness, an important quality in preventing mesh erosion (Dietz, 2003).

To further promote healing and tissue ingrowth, the density of the polypropylene can be reduced to create a "lightweight" mesh. These material properties were carefully evaluated before designating this product as the best available and selecting it for use for the TVT sling after having tried a variety of other synthetic

materials. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years (Nilsson, 2013). One cannot attach any clinical significance to claims of alleged particle loss and mesh degradation over time. Such claims are not supported by any level 1 evidence, nor have I experienced any complications attributable to alleged particle loss or degradation in my clinical practice. Given the large number of women who have been enrolled in clinical trials of various mid-urethral sling types, any correlation between materials and complications should be readily apparent.

In contrast, the choice of a macroporous, monofilament, polypropylene mesh tape as the most suitable material for use in mid-urethral slings is substantiated by strong clinical data (Cox, 2013; Ogah 2011, Ford 2015, Schimpf 2014, Tommaselli 2015). Monofilament tapes (of which TVT predominates) had significantly higher objective cure rates compared to multifilament tapes and fewer tape erosions (1.3% versus 6%, RR 0.25, 95% CI 0.06 to 1.00). It is important to note that the FDA and all leading urogynecologic professional societies have clearly stated and endorsed the fact that the safety and effectiveness of polypropylene mid-urethral slings is well established (FDA 2013; AUGS-SUFU position statement 2014; AUA position statement 2013; IUGA position statement 2014). AUGS-SUFU has further provided a written statement endorsing the safety of the sling material in their "Frequently asked questions of providers" physician manual. In response to the question: "What is the material used for mid-urethral slings and have studies shown the material to be safe? Response: "As the knitted form, polypropylene mesh is the consensus material as a graft augmentation layer for hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years."(AUGS, 2013). Additionally, the European professional guidelines have recognized TVT and TVT-O as the first line treatment option for women with stress urinary incontinence. (NICE 2013; EAU Guidelines 2015).

Mesh shrinkage following implantation in the abdominal wall has been noted in various animal studies where the mesh surface area can contract 25-30%. In an animal study evaluating the biomechanical properties of five prostheses used for pelvic floor repair, however, non-absorbable prostheses retracted least. Forces at rupture were disparate with a significant difference in favor of Prolene ($p < 0.001$). Furthermore, Dietz et al evaluated mid-urethral slings on ultrasound at a mean of 1.6 years post-implant. The TVT was not found to contract or shorten at all (Dietz, 2003). Based on these results, monofilament and macroporous propylene prostheses seem, after implantation, to have the best mechanical performance and best tissue integration (Boukerrou, 2007). Similar results showing no shrinkage or contraction with TVT in the short-term or long-term have been published (Nilsson 2013, Lo 2004, Dietz 2003, Lukacz 2003). In fact, a hernia mesh explant study found that Prolene mesh was the only mesh to show no shrinkage. (Coda 2002). I am aware of an internal email in which Dr. Axel Arnaud suggested using "30%

shrinkage as the rule of thumb." Dr. Arnaud explained in his deposition that shrinkage with TVT is a "theoretical risk, but it has not been a very practical risk." [Arnaud 7.19.13 at 121:11-15]. Dr. Arnaud elaborated in response to an attorney's questions about potential shrinkage with TVT: "…. You are explaining that the polypropylene mesh might retract, shrink, by 33 percent, which means that if you implant a 20 centimeter TVT, it should – if I follow you correctly, it should end up with being a 14 centimeter long sling, and this would result in urinary retention for all patients all over the world. So what we are talking about is completely different, and allow me to say that, totally inappropriate. And this slide is the best – is the best evidence that, you know, you can show me everything you want, but don't tell me that the slings used in TVT, which is a polypropylene mesh, is shrinking by 33 percent, because no one can accept that." [Arnaud 9.25.13 at 850:14-851:12]. Dr. Arnaud also testified that with TVT "there is no shrinkage with time." [Arnaud 9.25.13 at 790:21-791:14]. Dr. Arnaud explained how everything from the hernia literature cannot be extrapolated to the SUI literature: "My disagreement with you comes from the fact that you are trying to move from this, which is a paper about inguinal hernia repair, hernia repair, to something very different, which is the sling for incontinence." [Arnaud 9.25.13 at 804:10-805:2].

Mesh implantation in rats has also been used as the basis for claims of carcinogenic potential. Plaintiffs' experts have suggested that polypropylene is associated with sarcoma formation. Tumors related to the implantation of surgical grade polypropylene in humans have never been reported. Further studies have determined, however, that flat, continuous sheets of any material can induce sarcoma formation. The material itself is not associated with carcinogenesis but rather the shape and surface area that the material covers (McGregor 2000; Maolli,2014). Studies in which porous polypropylene mesh was implanted, as opposed to a continuous sheet, demonstrated no risk of malignancy for 2 years following implantation (Witherson, 2004). If even a small associated risk existed, one would expect that after 3 million sling implants, one should have observed a measurable increase in cancers. In a report issued by one of the leading experts in synthetic mesh materials in the world, Dr. Moalli concluded that polypropylene mesh is not associated with carcinogenesis (Moalli, 2014; King 2014).

The potential cytotoxicity of polypropylene mesh has also been raised as a potential safety concern. In vitro testing that accompanied the 510K FDA submission demonstrated some evidence of cytotoxicity but no in vivo testing raised clinical concerns. This information was presented and reviewed by the FDA within the context of available human data that showed clinical efficacy and safety. It stands to medical reason that a cytotoxic implant would lead to a consistent adverse host response with tissue necrosis, extensive inflammation, and rejection. While a fibrotic host response is occasionally observed, the vast majority of implanted women (at least 97%) demonstrate no adverse sequelae from the mesh almost 10 years post implant. The suggestion by plaintiffs' experts that TVT results in carcinogenic effects or adverse systemic effects associated with alleged cytotoxicity are not accompanied by any methodologically sound or scientific analysis, and is

completely lacking in clinical significance. Furthermore, the suggestion in a material safety data sheet (MSDS) that polypropylene discs implanted in rats induced sarcomas at the site of implantation cannot and has not been extrapolated to humans. Claims such as these are based on hyperbole and fear mongering with absolutely no scientific basis or fact.

Another claim that has been made is that polypropylene mesh degrades over time and this degradation contributes to an adverse host response. This hypothesis is most clearly stated in a French study where 100 synthetic meshes were explanted. It is unclear whether the initial meshes were placed for prolapse repair or for incontinence which may have significant clinical implications given the relative difference in mesh load. In 70% of explanted samples, the mesh material was exposed in vivo. Scanning electron microscopy showed that 42% of materials had evidence of "degradation" defined as peeling of the surface fiber, transverse cracks in the implant threads, cracks with disintegrated surfaces, and flaking. Given the high rate of exposure of the samples, it is unclear whether external mechanical forces, exposure to oxidation, or bacterial infection could be responsible for the observed changes (Clave, 2010). The importance of this interaction between polypropylene and the external environment was demonstrated by a study in 1974 in which polypropylene suture without an anti-oxidant package revealed degradation, whereas suture within an anti-oxidant package showed no degradation (Liebert, 1976). To further highlight the potential for mesh exposure itself being the reason for the observed electron microscopy findings, a study of 24 women undergoing partial sling excision in which the mesh was NOT exposed revealed no evidence of graft degradation. The polypropylene mesh explants were characterized by the greatest number of infiltrating fibroblasts, a favorable histologic finding that confirms healthy tissue ingrowth (Woodruff, 2008). Other authors have concluded that the surface cracking shown under SEM was really just a layer of cracked protein, likely as a result of a reaction with the formalin, that formed over the synthetic material. (De Tayrac 2011).

Finally, in the Clave study, there was no characteristic pattern of degradation observed in different mesh materials, an observation that speaks against a general problem with polypropylene degradation. Interestingly, the authors themselves stated that none of the hypotheses concerning degradation of polypropylene, "particularly direct oxidation, could be confirmed in this study."

Regardless of the debate about degradation, no study has proven that evidence of this "degradation" is associated with reduced tensile strength or any predictable host response. Stated simply, there is no level 1 evidence demonstrating any clinical significance to alleged degradation, or complications that arise due to degradation. Studies of explanted meshes from the abdominal wall in rats have also not demonstrated any evidence of product degradation. In addition, no electron microscopy studies have been conducted on "healthy" sling patients to determine what happens to the material properties in these women. It certainly comes as no surprise to me that mesh material that has been exposed in the vagina could have

different properties under a microscope than meshes that have successfully been incorporated into host tissue. Finally, the observations described on electron microscopy are not definitive evidence of mesh degradation and there is no correlation between these findings and a change in the mechanical and functional properties of the mesh. Given the proven efficacy of mid-urethral slings over a prolonged post-implant period, there is significant clinical evidence that the sling material remains fully functional.

Among all the mid-urethral slings, Ethicon's TVT sling has the most data and the longest follow up. There is no credible evidence that a larger pore mesh, such as the Ultrapro mesh used for prolapse repair, would be a superior material. There is only 1 published study that has even evaluated the use of Ultrapro mesh for mid-urethral sling. This study involved 144 women who were randomized to a combination absorbable/non-absorbable mesh (Group 1) vs Ultrapro mesh (Group 2) vs Prolene light-weight mesh (Group 3). There was no conformity to the size of the mesh implant that was fashioned for each individual patient. Essentially, a patch of mesh was attached to 2 polypropylene sutures that were then passed through the retropubic space and tied down to the rectus fascia. In this study, the claim was made that postoperative complications were lowest in the Ultrapro group. Review of the study data reveals that there were 2 cases of mesh erosion into the vagina and 1 case of urethral erosion in Groups 1 and 3 whereas there was 1 vaginal erosion in Group 2. Given the dramatic modification to the sling technique and the variance in size of the mesh implants, no credence can be attached to these small study numbers.

The material science of TVT mesh does prove that if undue tension is placed on the mesh material, and it is significantly stretched, then the sides of the sling can curl in and the mesh can assume the appearance of a "rope" as opposed to a flat piece of mesh. This scenario can be achieved if the tape is placed, the plastic sheaths are then removed, and significant tension is applied to the ends of the exiting sling in order to tighten the mesh. This technique is contrary to what is clearly outlined in the surgical steps of the IFU. If the tape is placed according to instructions provided in the IFU and through industry sponsored professional educational materials, this effect of curling or roping of mesh is not observed. High levels of force can safely be placed on the mesh system as long as the plastic sheaths remain intact. The clear plastic sheath surrounding the mesh is an important design characteristic of the TVT device. In addition to shielding the mesh from direct contact with the vaginal microbiome, the sheath protects the mesh from deformation during placement and tensioning. The incorporation of the sheath in the design transfers the load of forces during insertion and reduces tissue drag. The sheath facilitates placement and when removed, allows for inter-collation of the mesh into the surrounding tissues. Any written reference or photograph about results of the mesh being mechanically stretched without the sheath in place is not transferable to the techniques that should be employed in surgery.

An additional claim has been made that when mesh is cut mechanically as compared to with a laser, small particles can adhere to the mesh and induce an inflammatory and cytotoxic host response. Mechanically cut mesh was used for the TVT sling from 1998 until 2007, and continued to be made and sold even after the introduction of TVT utilizing a laser cut.. Ethicon still sells both mechanically cut and laser cut TVT in order to satisfy surgeon preferences. As we have rigorous clinical data from implants prepared using the 2 different techniques, there is robust opportunity to assess for any difference in outcomes. None have been observed. Overall, this theoretical risk has lead to no measurable clinical effect or risk.

D. Scientific investigation of TVT sling: Efficacy, durability, and safety.

TVT has become the new gold-standard procedure for the treatment of primary and recurrent SUI through rigorous and extensive scientific investigation. The TVT sling remains the most studied procedure in all of gynecology with more than 2000 publications in the scientific literature involving thousands of women. These studies include the highest level I scientific evidence (Ogah, 2009). Position statements in support of full-length mid-urethral slings for treatment of SUI have been released by ALL major national and international incontinence societies including AUGS, SUFU, AUA, IUGA, ICS, NICE, and the European Association of Urology. The medical literature evaluating mid-urethral slings is much more robust than literature that has evaluated the Burch colposuspension, autologous fascial slings, and other materials, such as Ultrapro (a partially absorbable mesh studied in only one clinical trial for the treatment of SUI) that plaintiffs' experts rely upon. In fact, until the release of the RCT comparing colposuspension and pubovaginal sling in 2007, despite decades of medical use, less than 800 women had been evaluated in well-designed trials. In 1996, Black and Downs concluded: "In light of the methodological shortcomings of most evaluative studies, evidence about the effectiveness of surgery for stress incontinence is weak; there is little information on the value of sling procedures; and valid and reliable data on the frequency of complications following surgery are lacking, so the safety of the procedures is unclear."

Efficacy

Initial studies evaluated the outcomes of TVT without direct comparison to other surgical options. Two-year efficacy rates of 84-90% were demonstrated in women with primary SUI (Ulmsten, 1998; Olsson, 1999; Nilsson, 2001), recurrent SUI (Rezapour & Ulmsten, 2001; Kuuva, 2003), mixed UI (Rezapour 2001), and intrinsic sphincter deficiency (Rezapour, 2001).

Longer-term cure rates were first published in 2005. Of 970 women who underwent TVT surgery 2-8 years prior, 760 (78% response rate) provided follow up data. Those women with a primary indication of SUI only had a persistent cure rate of

85%. Those with an initial diagnosis of mixed incontinence had a steady reduction in efficacy from 60% at 4 years to 30% at 8 years (Holmgren 2005). Similarly, Kuuva et al reported cure rates of 74% at 6 years post-operatively (Kuuva 2006). Of 306 women studied in Korea, 7- year outcomes were assessed and cure rates of 85% were reported (Hyun Song, 2009). In 2008, Nilsson et al reported on 11-year outcome data from 90 women initially implanted with the device. Subjective cure was reported in 77% whereas 90% had negative objective evidence of SUI (Nilsson 2008). This same cohort was again assessed in 2013 and 87% remained subjectively cured or significantly improved 17.5 years after implantation. Based on numerous studies, the efficacy and durability of the TVT sling appears to sustain over a prolonged post-operative evaluation.

In 2002, Ward and Hilton reported the first multicenter, randomized trial comparing TVT and colposuspension in 344 women with SUI. Overall, 66% of patients in the sling group versus 57% in the colposuspension group met the definition of cure, defined as a negative stress test on urodynamics combined with a negative pad test. Satisfaction rates of 85% and 82% were reported in the vaginal tape and colposuspension groups, respectively. Surgical time, peri-operative pain, hospital stay, voiding dysfunction, and return to normal activities were all significantly higher in the colposuspension group. TVT was only associated with a higher rate of intraoperative bladder perforation. At 6 months, only 1 subject was noted to have vaginal mesh erosion (Ward, 2002). In 2007, 5-year outcomes from the same study were reported. Cure was defined as a 1-hour negative pad test and was reported in 81% of women in the TVT group versus 90% in the colposuspension group. 3 women were noted to have mesh erosion into the vagina whereas a significantly higher number of women in the Burch group had new posterior/apical vaginal wall prolapse.

In 2010, a Cochrane review of 62 randomized or quasi-randomized controlled trials with 7101 women that included at least one trial arm with a synthetic sub-urethral sling operation was published (Ogah, 2011). Overall, synthetic slings appeared as effective as traditional slings (Risk Ratio (RR) 1.03, 95% CI 0.94 to 1.13) but with shorter operative time, less voiding dysfunction, and fewer ne novo urgency symptoms. Compared to Burch colposuspension, synthetic slings appeared to be as effective (RR 0.91, 95% CI 0.74 to 1.12) with fewer perioperative complications, less voiding dysfunction, shorter operative time and hospital stay but with higher intraoperative bladder perforation (6% vs 1%). See also complication tables from Novara 2008 Review.

In 2014, the Society of Gynecologic Surgeons (SGS) conducted a systemic review and meta-analysis of traditional pubovaginal versus mid-urethral slings. Subjective cure rates were more than 50% lower in the traditional sling group (OR 0.40, 95% CI 0.18-0.85). Based on these results, SGS recommended preferential use of mid-urethral slings (Schimpf, 2014) for SUI.

In terms of comparative studies between different types of retropubic slings, the TVT has been found to be superior. For example, when compared to the intravaginal slingplasty, the TVT had significantly better results (IVS OR 0.47, p=0.007) (Ford, 2015; Meschia 2006; Ulmsten 1996). When compared to the top-down retropubic approach, it was also found to be significantly more efficacious (SPARC OR 0.53) (Novara 2007). Complications related to the bottom up approach are also significantly less compared to the top down approach. In a follow up short-version Cochrane review, Ogah reported that the traditional TVT was associated with fewer bladder perforations (4.7% vs 8.5%, RR 0.55, 95% CI 0.31-0.98) and fewer tape erosions (0.7% vs 3.5%, RR 0.27, 95% CI 0.08-0.95) than the top-down approach (Ogah, 2011). Both TVT and TOT slings have been associated with high rates of patient satisfaction. In the randomized trial of these 2 techniques, 85% in the retropubic group and 90% in the transobturator group reported high levels of satisfaction (Wai, 2013).

Based on the observed risk of bladder perforation with blind passage of retropubic trocars of all types, modifications of the mid-urethral sling were considered and evaluated. The trans-obturator technique was developed as a means to bypass the retropubic space yet still provide mid-urethral support. Numerous direct comparative trials between TVT and TOT have been conducted. A systematic review and meta-analysis of 11 trials reported equivalence in subjective outcomes with a reduction in risk of bladder injury (OR 0.12; 95% CI 0.05 to 0.33) and voiding difficulties (OR 0.55; 95% CI 0.31 to 0.98) in the TOT group. Groin/thigh pain (OR 8.28; 95% CI 2.7 to 25.4) and vaginal mesh erosion (OR 1.96, 95% CI 0.87 to 4.39), however, were higher in the TOT group (Latthe 2007). In a recent Cochrane review that was published in 2015, 81 trials that evaluated 12,113 women were reviewed. Based on inclusion of 55 trials involving 8652 women, overall efficacy is equivalent between TOT and TVT with subjective cure ranging from 62-98% in the TOT group and 71-97% in the TVT group. As directly stated in the paper, "MUS procedures performed using the retropubic approach had higher morbidity when compared to trans-obturator, though the overall rate of adverse events remained low." (Ford 2015).

In an attempt to limit the morbidity of the Burch colposuspension, an attempt was made to perform the procedure laparoscopically. This modification still requires general anesthesia, the use of 3-4 smaller abdominal incisions, and has a steep learning curve due to the difficult suturing angles in the retropubic space. Comparative studies have reported significantly better objective (RR 1.15, 95% CI 1.06-1.24) but not subjective cure rates (RR 1.11, 95% CI 0.99-1.24) for TVT compared to laparoscopic Burch. In a randomized trial of 128 women between TVT and laparoscopic Burch, objective cure was significantly higher in the TVT group (94% versus 78%) which correlated with higher satisfaction in the mesh sling group (Valpas, 2014). Based on less results, I do not teach laparoscopic Burch procedures to any trainees.

Safety

All operations are associated with potential risk, and mid-urethral slings are not immune to this risk. Generally, the risks associated with the TVT procedure are not unique and are experienced with all anti-incontinence procedures (Schimpf, 2014; Chahila 1999, FDA 2013 Considerations for SUI Mesh; AUA 2013 Position Statement for SUI. Surgeons performing any incontinence procedure require knowledge of abdominal, retropubic, and vaginal anatomy in addition to comprehensive knowledge of bladder and urethral physiology. This knowledge is acquired through medical school, residency, and post-graduate training. This knowledge may be supplemented by new material contained within an industry sponsored IFU but these IFUs cannot replace traditional sources of learning.

In addition to learning how to perform each individual surgical procedure, surgeons are required to fully understand and recognize complications and management strategies for each intervention. These risks are outlined in surgical textbooks and scientific publications, are tested during surgical training, are discussed during workshops and seminars at regional and national meetings, and are routinely included as questions on major board certification examinations. All of these risks have long been reported in the medical literature and it is fully expected that surgeon users are familiar with all of these risks. Individual hospital credentialing boards grant privileges for incontinence surgery based on demonstration and certification of specific expertise that is gathered through traditional surgical training. Therefore, any surgeon granted privileges to perform a specific incontinence procedure should have demonstrated adequate knowledge of the procedural steps and associated potential complications. While industry sponsored publications such as product IFUs are required by the FDA, these documents do not serve as the single reliable source of information for implanting surgeons. In fact, based on my personal experience, discussion with colleagues, the medical literature, and procedures followed by credentialing and licensing boards, the warnings in the TVT IFU are clear, useful and adequate because they cover the general procedural steps and risks of the procedure. The IFU, however, cannot supplant all the other knowledge gleaned in surgical training and it is not designed to replace traditional sources of learning such as medical textbooks etc. Furthermore, it is my strong opinion that surgeons should critically evaluate the medical literature independent of all industry-sponsored publications to obtain the most unbiased source of information available. This is the purpose of peer-reviewed scientific evidence. When reviewing the content of the IFU, it is critical to keep in mind the target audience and purpose of the TVT IFU. I have reviewed the 1991 FDA labeling guidance for medical devices and have determined that the TVT IFU adequately and appropriately described the adverse reactions that may occur as part of the effect of the device.

Surgeons should not be taught how to perform specific procedures by anyone other than an experienced surgeon in their field who has specific knowledge about that procedure. When new products or procedures are introduced to the market, surgeons are obligated to seek necessary training before assuming responsibility for the implantation, and subsequent clinical management of their patient. For example, as mid-urethral slings were not included in the array of anti-incontinence procedures that I was taught in my residency program, I traveled to Europe to first observe, and then scrub with a surgeon with extensive experience in TVT implantation. I felt it was my responsibility as the implanting surgeon to independently learn as much about the device and the technique before I could offer it to a patient. As described above, a baseline level of knowledge that is established during medical school and residency is necessary before adopting new procedures. For example, it is obvious to any surgeon who performs incontinence procedures that surgical instruments like the TVT trocar can lead to organ, vessel, and nerve damage, all of which could potentially lead to chronic pain. It is further obvious that wound complications such as granulation tissue, pain (temporary or permanent), dyspareunia, dehiscence, and infection can occur with any of these procedures. Similarly, complications such as mesh erosion and exposure have been well know and well documented in the medical literature since surgeons began using mesh for hernia repairs, prolapse repairs, and incontinence repairs, all of which pre-dated TVT. It remains the responsibility of the operating surgeon to completely understand the inherent risks of any surgical procedure before consenting a patient and proceeding with surgery.

Intraoperative complications

Intraoperative injuries include perforation of the bladder, lateral vaginal epithelium, urethra, hemorrhage from vessels in the retropubic space and/or groin, and bowel injury. Complications are often dependent on surgeon experience and volume (Welk 2015). For example, the risk of bladder perforations with TVT is lessened in the hands of more experienced surgeons. It is detected by routine intraoperative cystoscopy using a 70-degree cystoscope, a step that has always been deemed imperative. If a trocar is detected within the bladder lumen or is thought to be in the bladder wall, it is easily removed and replaced further laterally without any adverse sequelae. Unlike the more extensive bladder injuries that occur with either the Burch or pubovaginal slings, intraoperative TVT bladder perforation heals spontaneously without any need for post-operative bladder drainage.

Urethral injury is very uncommon, with a reported median rate of 0.88% (Daneshgari, 2008). The risks of both bladder and urethral injury have been decreased with extensive hydrodissection. Despite the blind passage of trocars retropubically, bowel injury occurs in less than 1% of TVT cases compared with 3.13% of Burch procedures (Schmipf 2014). Surgical hemorrhage is rare and occurs

in less than 2% of cases (Shah 2012). Mean operative blood loss is significantly less than with either Burch or pubovaginal slings (Albo, 2007 and Albo, 2012).

It is important to note that these complications occur in all procedures for stress incontinence and are not unique to mid-urethral slings. In fact, when complications are directly compared, the TVT appears safer than either the Burch procedure or pubovaginal sling. The recent systematic review conducted and published by the Society for Gynecologic Surgeons Systematic Review Group reported that mid-urethral slings result in lower rates of perioperative adverse events such as blood loss, operating room time, bowel injury, DVT, wound infections, urinary retention, and post-operative pain compared to the Burch colposuspension (Level I C evidence). When mid-urethral slings were compared to pubovaginal slings, the TVT resulted in shorter operative time, less blood loss, transfusion, wound infection, urinary retention, DVT, hospital stay, and overactive bladder symptoms. Pubovaginal slings only had a lower rate of urinary tract infection and vaginal perforation. A meta-analysis of adverse event information showed no significant difference in return to the operating room for sling erosion and favored the mid-urethral sling for better subjective cure rates (Schmipf, 2014). This comprehensive meta-analysis summarily dismisses many of the claims made by Dr. Blaivas in his published review entitled "Safety considerations for synthetic sling surgery." In this paper, Dr. Blaivas promotes the argument that mid-urethral slings carry greater risk than historical incontinence procedures. This simply is not a true statement.

Urethrovaginal fistulae are a recognized complication of any incontinence surgery.

Voiding dysfunction is a recognized complication of all types of incontinence surgery. How to manage this complication is under the direct jurisdiction of the implanting surgeon. The SGS Systematic Review Group's 2014 systematic review and meta-analysis, for instance, noted the following rates of retention following various incontinence procedures, including retropubic midurethral sling procedures like the TVT:

	Retropubic MUS	Burch	Pubovaginal Sling
Retention lasting < 6 weeks post-op	3.1%	17%	12%
Retention lasting > 6 weeks post-op	2.7%	7.6%	7.5%

Mesh exposure

Upon the introduction of the TVT, gynecologic and urologic surgeons had relatively little experience with the use of synthetic sling materials. Synthetic slings attached to retropubic bone anchors were introduced in the mid 1990's but were not widely used. The decision to use a permanent, synthetic material as opposed to autologous fascia introduced the unique risk of mesh exposure. The primary motivation behind the choice of a permanent material was to provide a stable platform of support that did not weaken or degrade over time and eliminate the need to harvest autologous fascia from the lateral thigh or abdomen- procedures that are associated with surgical morbidity due to wound infection and prolonged operative times.

As stated earlier, one of the primary reasons for my later adoption of the TVT sling, was my lack of knowledge of materials science and my concern about how women would react to sling implantation many years later. As more scientific literature was published on sling materials and longer term outcomes became available, I felt confident that theoretical issues such as sling degradation, fraying, curling, and retraction had no clinical significance and could be safely implanted in the majority of women. The quality and number of studies evaluating the long term safety and efficacy continues to grow at an impressive rate and has continued to reaffirm these findings.

Mesh exposure is a unique complication of mid-urethral slings compared to Burch colposuspension and autologous pubovaginal slings. In a large population based analysis of 188,454 eligible women who underwent an index sling, 3.7% required mesh revision/removal by 9 years. With regard to the indication for the sling revision/removal, a greater proportion was due to mesh erosion compared with urinary retention, with a 9-year risk of 2.5% (95% CI, 2.3-2.6) for mesh erosion vs 1.3% (95% CI, 1.2-1.4) for urinary retention. Age had an effect on the revision/removal rates for both mesh erosion and urinary retention, with the higher risks among those aged 18-29 years (Jonsson Funk, 2013). It should be noted that 97% of all women were doing very well with the sling implant almost 10 years postoperatively.

Mesh erosion is a well-known potential complication of any procedure involving surgical mesh. The rate of erosion following the TVT procedure is low, and has been estimated to be approximately 1%–2% (Novara 2008, Ford 2015). The rate of return to the operating room for an erosion following a retropubic sling procedure like the TVT is only 1.9% (Schimpf 2014). It is well known that smoking decreases oxygenation of tissue and negatively affects wound healing.

These results have been corroborated by several other studies. Large retrospective analyses and meta-analyses have consistently demonstrated a reoperation rate of 2.5 – 3.5% of patients studied out to 10 years (Welk, 2015; Unger 2015; Schimpf,

2014; Laurikainen 2014; Nguyen 2012; Ogah 2009; Novara 2008). I always remind my patients that an uncommon event that is multiplied by a factor of 3 million results in a total number of complications that is appreciable. Together, we decide whether they are willing to assume this known risk and whether these risks outweigh the potential benefit. After extensive counseling and evaluation, most women make the joint decision to proceed.

The need for post-operative sling revision for any cause, however, is not unique to synthetic mesh. In fact, in a retrospective cohort study of medicare beneficiaries who underwent slings, 19.3% of those with non-mesh slings versus 13% of mesh slings ($p<0.01$) required postoperative procedures for postoperative bladder outlet obstruction within 12 months. In a subset analysis, a higher percentage of women required sling removal or revision or urethrolysis procedures in the nonmesh group compared with the mesh group (4.7% versus 2.7%, $p=0.03$) (Oliphant 2009).

The correction of voiding dysfunction in women following a mid-urethral sling is far easier than following Burch or fascial sling. In the vast majority of cases, the mesh can be simply incised through a small vaginal incision. In contrast, trying to address retention following a Burch requires repeat entry into the retopubic space through a larger abdominal incision and is associated with risks of bleeding, bladder injury, and persistent retention. Vaginal mesh exposure is similarly easy to manage. In the vast majority of cases, the exposed mesh is simply excised, the overlying vaginal epithelium is mobilized and is then reclosed over the remaining mesh. This can be done with local anesthesia and surgical morbidity is extremely low.

Erosion of permanent material into the bladder is also not unique to mesh slings. Burch colposuspension and pubovaginal slings have both been associated with permanent suture erosion into the bladder and urethra (Schimpf 2014; AUA Guideline Appendices 2012).

Dyspareunia and pelvic pain

Chronic pelvic pain in women who have never had surgery is common enough to warrant an entire sub-specialty within Ob/Gyn (Steege & Mathias, 1996). In the post-surgical gynecology population, painful intercourse is a complicated problem that can be caused by a variety of factors in any post-surgical population. In fact, up to 20% of women report dyspareunia following vaginal hysterectomy (Abdelmonem, 2010). Potential causes include vaginal atrophy and resultant vaginal contraction, vaginal scarring following suture closure of the anterior vaginal wall, pelvic floor hypertonus, and complications specifically related to an implanted foreign body. In these cases, dyspareunia may be a result of mesh exposure, mesh infection, or tissue fibrosis. For women undergoing mid-urethral slings, however, sexual function overall has been noted to improve significantly. In a planned

secondary analysis on the randomized trial of TVT versus TOT (TOMUS trial), dyspareunia decreased from 38% at baseline to 27% at 2 years and overall function was much improved (Zyczynski, 2012; Wai 2013).

Dyspareunia and vaginal pain with TVT is rare and actually less than has been reported with Burch and fascial sling (Schimpf, 2014 ; AUA Updated SUI guidelines 2012). For mid-urethral slings, rates of post-operative dyspareunia have been reported in 0-6.2% of cases (Shah, 2012) with an average rate of 4.3% (Stanford 2008). It is important to note that studies regarding outcomes of mid-urethral slings typically include an evaluation of post-operative dyspareunia and pain whereas many of the older publications on Burch and pubovaginal sling focused on incontinence and voiding dysfunction.

Pelvic pain and thigh/groin pain have been reported with significantly higher rates in women undergoing TOT compared to TVT procedures. This is likely explained by the passage of the mesh through the muscles of the inner thigh. Persistent pain in the groin or thigh occurs infrequently with the retropubic TVT procedure, ranging from 1.5% to 2.6% (Laurikainen 2007; Latthe 2010). The majority of studies demonstrate that the leg or groin pain resolves spontaneously or with the use of mild analgesics.

A 2015 Cochrane Review by Ford and colleagues found that both retropubic and transobturator slings caused a significant improvement in sexual function from baseline scores, and that at 24-month follow-up, rates of superficial and deep dyspareunia were low in both cohorts (Ford 2015). In a study by Shah and colleagues, the retropubic sling fashioned by the authors using Ethicon's TVT mesh did not have a negative effect on sexual function (Shah 2005). Rates of chronic dyspareunia, pelvic pain, or vaginal pain following midurethral sling procedures such as those utilizing the TVT device are very low (Tommaselli 2015, Ford 2015).

Chronic pelvic pain is the most commonly experienced pain associated with endometriosis, but many women also have deep dyspareunia due to their endometriosis (Denny and Mann 2007).

Since the widespread advertisement of litigation regarding all mesh-based pelvic floor products, I have personally seen a dramatic increase in patient's seeking consultation for complaints of pain and dyspareunia. It seems striking that there is direct correlation in time between the onset of these complaints and the potential for secondary gain. Rates of mesh revision for the primary indication of pain have been very low in the scientific literature (Tommaselli 2015). For example, in Europe, Tamussino reported on the results of an Austrian Registry of 2795 patients of which 2.4% required repeat surgery for reasons related to the tape. The most common indication was for voiding dysfunction. In this large series, there was not a single reported case of surgical revision for pelvic pain, dyspareunia, or vaginal scarring. In the United States, Unger et al reported that of 3307 women who

underwent sling placement, only 7 (0.2%) subsequently required mesh removal for pain or dyspareunia.

Overall, the data from large prospective and retrospective series, randomized trials, and national registries do not support the claims that the TVT sling places women at a significant risk of long term, chronic complications or the need for reoperation.

Summary of scientific evidence

From 2000 to 2009, the rate of sling procedures increased from 209.7 to 266.5 per 100,000 person years (Johnsson Funk, 2012). Over 3 million mid-urethral slings have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members (Clemons, 2013). An analysis of case logs from certifying American urologists in 2013 reported that traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 and to <1% since 2010 (Chughtai, 2013).

The rapid and widespread uptake of mid-urethral slings likely represents surgeon and patient preference for a minimally-invasive procedure that can be performed under local anesthesia in less than 30 minutes with a short recovery and minimal post-operative pain. The widespread enthusiasm and adoption of the procedure is supported by the strongest scientific evidence which concludes that TVT is reasonably safe for its intended use; TVT is as effective than alternative surgeries, but is less morbid, with a quicker operative and recovery time. The original retropubic TVT sling stands alone in the field of urology and gynecology as the most extensively studied anti-incontinence procedure in history. The extended durability of the procedure far outweighs the operative risks of the procedure and the longer term risks of mesh revision for mesh exposure or voiding dysfunction. The medical evidence clearly proves that women are more likely to need revision following a pubovaginal sling than they are following a TVT. The complications from TVT are well-known and acceptably low; especially when compared to alternative, more invasive surgeries for SUI. The complications of TVT slings are not unique

In 2013, the FDA confirmed that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." The original retropubic TVT sling stands alone as the most extensively studied anti-incontinence procedure in history- scientific methodology has been robust and rigorous and outcomes have been transparently reported. Importantly, women have been extensively followed over time, up to 17 years post implant. Clinical practice guidelines from AUA, AUGS, SGS, IUGA, and ICS strongly endorse the primary use of mid-urethral slings for SUI. The commitment to diligently evaluating and reporting outcomes has allowed skeptical surgeons like myself to fully embrace this surgical technique and this technology as the best surgical option for SUI management. It has clearly assumed the position of the new "gold-standard".

The robust scientific literature findings are best summarized in the practice bulletin jointly published by ACOG and AUGS: "Mid-urethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with mid-urethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic mid-urethral slings." (ACOG Practice Bulletin Number 155, 2015).

I have been a steward for patient safety, autonomy, and justice throughout my medical career. I have always been cautious and conservative in my treatment approach and have not been swayed by popular opinion in the absence of medical evidence. For example, due to the paucity of medical evidence that demonstrates a significant benefit over risk, I have never been an advocate of vaginal mesh procedures for pelvic organ prolapse repair. With regards to mid-urethral slings, I learned the historical procedures, offered them to patients when appropriate, and only adopted this new technology once robust data was available to support its use. In the face of aggressive solicitation from lawyers, I continue to offer mid-urethral slings as my first-line treatment for stress incontinence as the procedure with the most favorable benefit to risk profile.

Complications are well-known to pelvic floor surgeons performing surgeries to treat SUI

The only unique risk associated with TVT compared to Burch and Autologous Fascial Slings is the risk of mesh erosion or exposure. All other risks, including their frequency and severity, are or should be well-known to any pelvic floor surgeon performing these procedures to treat SUI. On October, 20, 2008, the FDA issued a public health notification for POP and SUI meshes which included the following warning to surgeons: "The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.... Specific characteristics of patients at risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status." The FDA suggested that pelvic floor surgeons do the following:

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.

- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."

In 2013 the FDA also notified pelvic floor surgeons about the results of its systematic review of the published scientific literature from 1996 to 2011, which included information about well-known risks of synthetic meshes, including:

- The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one year...
- The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI, which is mesh erosion, also known as extrusion.
- Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of mesh erosion, it may be necessary to return to the operating room to remove part of all of the mesh.
- The long-term complications of surgical mesh sling repair for SUI that are reported in the literature are consistent with the adverse events reported to the FDA....
- The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI."

The AUA noted in its 2011 and 2013 position statements on the use of vaginal mesh for the surgical treatment of SUI that "mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-

mesh sling procedures as well."

The adverse reactions section of Ethicon's various TVT IFUs did not change until 2015. The TVT has always warned of the following: (1) Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair; (2) Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation; (3) As with all foreign bodies, Prolene mesh may potentiate an existing infection. The plastic sheath initially covering the Prolene mesh is designed to minimize the risk of contamination; and (4) Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

21 Code of Federal Regulations 801.109(c) permits a manufacturer to omit from its labeling information or risks that are "commonly known to practitioners licensed by law to use the device." Additionally, Ethicon's Standard Operating Procedure for Regulatory Labeling provides in Section 6.1.2: "Labeling must convey the information that end-users need to safely use the device as intended by the manufacturer, taking into account the conditions of use and any issues that may be specific to the type of device." Mesh erosion or exposure is the only risk that is unique to TVT, and even then, Burch and Autologous slings still share the risk of suture or graft erosion or exposure. The Amid type I Prolene mesh material, route of implantation, and the frequency and severity of complications associated with TVT are well known to surgeons who are the intended users of the TVT. Similarly, pelvic floor surgeons who perform stress urinary incontinence surgeries are aware of the common set of complications that can occur from Burch procedures and suburethral slings, regardless of the type of suture or graft material used. Temporary or long-term pain, scarring, and dyspareunia are not unique to TVT or midurethral slings, but are well-known complications of any pelvic floor surgery. Surgeons are taught about the risks associated with foreign body implants and potential complications from stress urinary incontinence surgeries in medical school, residency, and fellowships. The set of complications, as well as the frequency and severity of complications, have been published and discussed in numerous medical textbooks, peer-review publications, book chapters, editorials, systematic reviews, FDA public health notices, meeting abstracts, conference materials, professional society publications, continuing medical education events, board certification study guidelines and tests, etc. Risks associated with stress urinary incontinence surgeries, including risks of foreign body implants and their properties, are part of basic set of knowledge that is learned throughout medical school, residency, and fellowship, as well as tested on the board and subspecialty board exams.

The IUGA 2010 Guidelines for Training in Female Pelvic Medicine and Reconstructive Surgery sates that the trainee should receive experience in the theory, practice and performance of minimally invasive slings, including retropubic

midurethral slings, mesh used in repair, use of various graft materials, and removal of mesh/sutures.

The jointly sponsored ABOG and ABU Guidelines for Learning in Female Pelvic Medicine and Reconstructive Surgery states that fellows should be able to perform retropubic synthetic slings and be able to identify, evaluate, and manage complications associated with continence surgery, including foreign body associated complications. Fellows are also expected to discuss: (1) different types of graft materials used in prolapse and incontinence surgeries, including graft properties, advantages, and risks associated with each graft; (2) the relevant characteristics (pore size, filament type, flexibility, tensile strength) or augmented surgical materials; and (3) the level of evidence (success and complications) for the use of augmenting surgical materials for prolapse and incontinence surgery.

The ACGME Program Requirements for Graduate Medical Education in FPMRS states that Fellows must demonstrate competence in performing synthetic slings, and must demonstrate competence in their knowledge of indications, contraindications, limitations, complications, and techniques for urinary incontinence procedures.

The AUGS Resident Learning Objectives requires that residents understand and be able to perform midurethral slings, and should be able to discuss risks, benefits, and expected outcomes of nonsurgical and surgical management of SUI. Residents are also expected to understand the indications for use of graft materials in pelvic surgery and their potential complications. Residents are expected to understand: (1) the categories of graft materials, such as biografts and synthetic grafts; (2) the vital characteristics of synthetic grafts, such as pore size, mono versus polyfilament, and material types; (3) the relative indications for and complications associated with each graft; and (4) the management of graft complications, both surgical and non-surgical. Residents are expected to be familiar with the graft materials references, including: Davila 2005, Dwyer 2006, Deprest 2006, Huebner 2006, Silva 2005, Culligan 2005, Paraiso 2006, and Gandhi 2005. Residents are also expected to be familiar with the following TVT and SUI literature: Ulmsten 1995, Ulmsten 1998, Olsson 1999, Mutone 2001, Rezapur 2001, Leache 1997, Black 1996, Van Geelen 1988, Tanagho 1976, Columbo 1994, Columbo 1997, Bowen 1989, Wiskind 1992, Shull 1989, Marinkovic 1998, Appell 1998, and Nilsson 2001, to name a few.
My education, training, clinical experience, discussions with colleagues, and extensive contributions to and review of the peer reviewed medical literature do not support plaintiffs' experts' suggestions that the TVT design or IFU are in any way defective or inadequate due to theoretical risks of roping, curling, fraying, particle loss, degradation, contraction and shrinkage, cytotoxic, pore collapse, or chronic foreign body reaction. These mechanisms do not lead to clinically significant complications and therefore there is no reason for Ethicon to warn of theoretical risks. The statement in the IFU about "the material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes" is accurate according

to my clinical experience, my discussions with colleagues, and my thorough review of the medical literature. For example, this statement is supported by the 1967 Miller study, which states that polypropylene "is also resistant to the action of tissue enzymes," as well as the previously mentioned studies (Miller 1967). While there may be some recent debate in the literature about whether degradation occurs, there is no evidence that degradation or particle loss is of any clinical significance in that it causes complications or failure.

Ethicon added a number of adverse reactions to the TVT IFU in 2015, but all of these risks are commonly known to experienced pelvic floor surgeons who are the intended users of the IFU. The risks listed in Ethicon's 2015 TVT IFU are all commonly known risks, which can be temporary or long-term, and only mesh erosion or exposure is unique to TVT. These commonly known risks, some more rare than others, include:

- Punctures or lacerations of vessels, nerves, structures or organs, including the bladder, urethra or bowel, may occur and may require surgical repair.
- Transitory local irritation at the wound site may occur.
- As with any implant, a foreign body response may occur. This response could result in extrusion, erosion, exposure, fistula formation and/or inflammation.
- Mesh extrusion, exposure, or erosion into the vagina or other structures or organs.
- As with all surgical procedures, there is a risk of infection. As with all foreign bodies, Prolene Mesh may potentiate an existing infection.
- Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.
- Acute and/or chronic pain.
- Voiding dysfunction.
- Pain with intercourse which in some patients may not resolve.
- Neuromuscular problems, including acute and/or chronic pain in the groin, thigh, leg, pelvic and/or abdominal area may occur.
- Recurrence of incontinence.
- Bleeding including hemorrhage, or hematoma.
- One or more revision surgeries may be necessary to treat these adverse reactions.
- Prolene Mesh is a permanent implant that integrates into the tissue. In cases in which the Prolene Mesh needs to be removed in part or whole, significant dissection may be required.
- Seroma.
- Urge incontinence.
- Urinary frequency.
- Urinary retention.
- Adhesion formation.

- Atypical vaginal discharge.
- Exposed mesh may cause pain or discomfort to the patient's partner during intercourse.
- Death.

Ethicon's TVT IFUs appropriately warns surgeons of adverse events that are specific to the device. The risks that are listed in the 2015 TVT IFU are and have been commonly known risks to pelvic floor surgeons for decades. This is based on my education, training, clinical experience, discussions with colleagues, constant review of medical literature and textbooks, attendance at professional society meetings and continuing education events, experience as a peer reviewer for medical journals, experience training residents and fellows, and my experience with licensing exams.

In conclusion, level 1 clinical data supports the safety and efficacy of TVT. Similar or superior clinical data for a partially absorbable sling using Ultrapro does not exist. While there is no risk-free surgical procedure, the benefits and the utility of TVT significantly outweigh the potential risks. All of the major professional societies, including, AUGS, ACOG, SUFU, AUA, EAU, IUGA, NICE, have recently endorsed the synthetic midurethral sling as the gold standard or standard of care for treating stress urinary incontinence through position statements and/or practice guidelines.

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DATE: June 1, 2016